EASTMAN

Eastman Chemical Company
P. O. Box 431
Kingsport, Tennessee 37662

8EHQ_0399_14391

February 19, 1999

Document Control Office (7407)
Attn: TSCA Section 8(e)
Room G99 East Tower
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460-0001

8EHQ-99-14391
88990000110

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ladies and Gentlemen:

Eastman Chemical Company submits two reports as required under TSCA §8(e) for your consideration.

1.	(Preliminary)	Eye Irritation Study of Cyclopropyl Methyl Ketone in the Rabbit
2.	(Final)	Cyclopropyl Methyl Ketone: Acute Dermal Irritation Study in the Rabbit

If you have questions, you may contact me by telephone at (423) 229-4274 or the technical contact, Karen R. Miller, Ph.D., at (423) 229-1654.

Very truly yours,

F. David Petke

F. David Petke, Ph.D.
Senior Technical Associate
Product Safety and Stewardship

Contains No CBI

cc: 8(e) file

8(e)1999-1.doc

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A Public Commitment

TSCA HEALTH & SAFETY STUDY COVER SHEET - revised 6/25/96

TSCA CBI STATUS:

☐ **CHECK IF THIS PAGE CONTAINS CONFIDENTIAL BUSINESS INFORMATION (CBI)**

Clearly mark the confidential information with bracketing and check the box in the appropriate section (☐ *Contains CBI*). Submit a sanitized cover sheet with CBI deleted. Mark the sanitized copy, "Public Display Copy" in the heading.

1.0 SUBMISSION TYPE ☐ *Contains CBI* Submission date: February 19, 1999

☐ 8(d) X 8(e) ☐ FYI ☐ 4 ☐ Other: specify

X Initial submission ☐ Follow-up submission ☐ Final report submission

Previous EPA Submission or Title if Update or Follow-up: Docket Number, if any: #

☐ continuation sheet attached

99 MAR -1 PM 3:34 RECEIVED OPPT CBIC

2.1 SUMMARY/ABSTRACT ATTACHED	2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID	2.3 FOR EPA USE ONLY
X Yes ☐ No	8(e)1999-1	

3.0 CHEMICAL/TEST SUBSTANCE IDENTITY ☐ *Contains CBI*

Reported Chemical Name (specify nomenclature if other than CAS name):

CAS #: 765-43-5 Ethanone, 1-cyclopropyl

Purity: 100 %

X Single Ingredient

☐ Commercial/Technical Grade

☐ Mixture Trade Name: None Common Name: cyclopropyl methyl ketone

	CAS Number	*Nam*	*% WEIGHT*
Other chemical(s) present in tested mixture	None		

☐ continuation sheet attached

8EHQ-99-14391

4.0 REPORT/STUDY TITLE ☐ *Contains CBI*

Cyclopropyl Methyl Ketone: Acute Dermal Irritation Study in the Rabbit

☐ continuation sheet attached

88990000110

5.1 STUDY/TSCATS INDEXING TERMS

[CHECK ONE]

HEALTH EFFECTS (HE): X ENVIRONMENTAL EFFECTS (EE): ENVIRONMENTAL FATE (EF):

5.2 STUDY/TSCATS INDEXI NG TERMS (see instructions f or 4-digit codes)

STUDY	SUBJECT ORGANISM	ROUTE OF	VEHICLE OF
TYPE: DIRR	(HE,EE only): RABB	EXPOSURE (HE only): DERM	EXPOSURE (HE only): Other
Other:	*Other:*	*Other:*	*Other: 100% substance*

6.0 REPORT/STUDY INFORMATION ☐ *Contains CBI* *X Study is GLP*

Laboratory: Health and Environment Laboratories, Eastman Kodak Company 1100 Ridgeway Avenue, Rochester, NY 14652 Report/Study Date: Feb 04, 1999

Source of Data/Study Sponsor (if different than submitter) Number of Pages: 13

☐ continuation sheet attached

7.0 SUBMITTER INFORMATION ☐ *Contains CBI*

Submitter: Marc G. Schurger Title: Director, Product Safety and Stewardship Phone: (423) 229-5921

Company Name: Eastman Chemical Company Company Address: P. O. Box 431, Kingsport TN 37662-5280

Submitter Address (if different):

Technical Contact: Karen R. Miller, Ph.D. CONTAINS NO CBI Phone: (423) 229-1654

☐ continuation sheet attached

8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS ☐ *Contains CBI*

However, it should also be noted that in the dermal toxicity study in rats, a single limit dose of 2000 mg/kg resulted in no irritive effects. In the skin sensitization study in guinea pigs, a 10% solution caused no signs of irritation. And finally, in an *in vitro* skin absorption test using human skin, no significant damage to the skin was seen after exposure to the test substance for 8 hours.

☐ continuation sheet attached

Submitter Signature: Marc G Schurger Date: 2/18/99

9.0 CONTINUATION SHEET

TSCA CBI STATUS:

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Submitter Tracking Number/Internal ID

8E-1999-1

Preliminary Results for Cyclopropyl Methyl Ketone Dermal Irritation Study in the Rabbit

A dermal irritation study was conducted by administering single topical doses of 0.5 mL of the test substance to three rabbits. The test substance was left in contact with the skin under an occlusive wrap for four hours. Two of the three rabbits had signs of irritation limited to erythema (grade 1)[1] at the 1-hour examination. One of these two rabbits still had grade 1 erythema at the 24-hour examination and the other rabbit was normal. At the 48 hour examination, both rabbits had returned to normal. For the remaining rabbit, erythema (grade 3) and necrosis were observed at the application site 1 hour after termination of exposure. At the 24-hour examination, erythema (grade 3), edema (grade 1), and necrosis were noted. At the 48- and 72-hour examinations, edema (grade 1) persisted and eschar formation (erythema- grade 4) was noted over the previous area of necrosis. Erythema (grade 2) was present at the margins of the eschar. On day 7 of the study, only a scar was seen at the application site and the study was terminated.

The irritative effect of the test material was supported by the observation in the acute oral toxicity in rats. No treatment-related changes were observed at necropsy for animals which survived to termination of the study. For animals which died or were euthanatized, treatment-related changes provided evidence that the test substance was a gastric irritant. These changes included necrosis, hemorrhage, and hyperkeratosis of the gastric mucosa and the presence of blood in the stomach, duodenum and jejunum.

A copy of the final report is attached.

[1]Graded according to OECD Guideline 404 (Annex V., Test B.4)

FINAL REPORT

CYCLOPROPYL METHYL KETONE
SYNONYM: 1-CYCLOPROPYLETHANONE

PM No.: 20644-00 **CAS No.: 000765-43-5**
HAEL No.: 98-0264 **EAN: 905571**

ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

GUIDELINE

OECD: 404
EEC: Annex V., Test B.4

AUTHOR

Stephen D. Jessup, A.A.S.

TESTING FACILITY

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

98-0264A2

STUDY SPONSOR

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280

STUDY COMPLETION DATE

February 4, 1999

QUALITY ASSURANCE INSPECTION STATEMENT
(21 CFR 58.35(B)(7), 40 CFR 792.35(B)(7), AND 40 CFR 160.35(B)(7))

STUDY: 98-0264-1 STUDY DIRECTOR: SHEPARD,K.P. PAGE 1
ACCESSION NUMBER: 905571 01/22/99

STUDY TYPE: ACUTE DERMAL IRRITATION TEST

M. L James 1/22/99
(AUDITOR, QUALITY ASSURANCE UNIT) DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT. WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES.

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
10/13/98	PROTOCOL APPENDIX/AMENDMENT SUBMISSION	
10/15/98	CLINICAL SIGNS AT 48 HRS.	01/22/99
01/22/99	FINAL REPORT REVIEW	01/22/99

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted according to:

Annex 2, Organisation for Economic Cooperation and Development, Guidelines for Testing of Chemicals [C(81)30(Final)].

Kenneth P. Shepard, B.S.
Study Director

February 4, 1999
Month/Day/Year

SIGNATURE PAGE

Stephen D. Jessup, A.A.S.
Report Author

January 22, 1999
Month/Day/Year

Kenneth P. Shepard, B.S.
Study Director

February 4, 1999
Month/Day/Year

Douglas C. Topping, Ph.D.
Unit Director, Mammalian Toxicology

Jan 27, 1999
Month/Day/Year

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ABSTRACT

CYCLOPROPYL METHYL KETONE
SYNONYM: 1-CYCLOPROPYLETHANONE

PM No.: 20644-00 **CAS No.: 000765-43-5**
HAEL No.: 98-0264 **EAN: 905571**

ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

A dermal irritation study was conducted by administering single topical doses of 0.5 milliliter of the test substance to rabbits. The test substance was left in contact with the skin under an occlusive wrap for four hours. Skin lesions were graded according to OECD Guideline 404 (Annex V., Test B.4).

For two of three rabbits, signs of irritation were limited to erythema (grade 1) at the 1-hour examination or the 1-hour and 24-hour examinations. For the remaining rabbit, erythema (grade 3) and necrosis were observed at the application site one hour after termination of exposure. At the 24-hour examination, erythema (grade 3), edema (grade 1), and necrosis were noted for this rabbit. For the 48- and 72-hour examinations, edema (grade 1) persisted while eschar formation (erythema -grade 4) was noted over the previous area of necrosis. Erythema (grade 2) was present at the margins of the eschar. On Day 7 of the study, only a scar was seen at the application site and the study was terminated.

Based on necrosis observed at the application site of a single rabbit after a 4-hour exposure, the test substance is considered to be corrosive to the skin and labeled as "causes burns" as defined in the 18th Adaptation of the EC Classification, Packaging, and Labelling of Dangerous Substances Directive.

STUDY AND TEST SUBSTANCE INFORMATION

Testing Facility

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

Project Participants

Study Director:	Kenneth P. Shepard, B.S.
Principal Investigator:	John W. Mosher, B.S.
Report Author:	Stephen D. Jessup, A.A.S.

Sponsor

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280

Sponsor's Representative:
Karen R. Miller, Ph.D.

Test Substance Characterization

Test Substance Identity:	Cyclopropyl methyl ketone
Synonym:	1-Cyclopropylethanone
CAS No.:	000765-43-5
PM No.:	20644-00
EAN:	905571
HAEL No.:	98-0264
SRID or Lot No.:	X26270-41
Physical State and Appearance:	Liquid, Clear
Source of Test Substance:	Eastman Chemical Company
Laboratory Project ID:	97-0264A2

Study Dates

Study Initiation Date:	October 13, 1998
Experimental Start Date:	October 13, 1998
Experimental Completion Date:	October 20, 1998

PURPOSE

The purpose of the study was to determine the potential of the test substance to cause primary irritation of mammalian skin.

MATERIALS AND METHODS

Test system

Three albino rabbits (Hra:(NZW)SPF) obtained from Covance Research Products Inc. (Denver, PA) were assigned to the study. The rabbits were young adults (at least three months old) and weighed at least 2000 grams at the start of the study. Rabbits were chosen for this study because they are a common representative species for dermal irritation studies. The rabbit is the preferred species recommended for use in the OECD Guideline.

Husbandry

Housing

Animals were housed in an Association for Assessment and Accreditation of Laboratory Animal Care International accredited vivarium in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). The rabbits were singly housed in suspended, stainless-steel mesh cages. Cages and racks were washed once a week. Absorbent paper, used to collect excreta, was changed every other day.

Environmental Conditions

The study room was maintained at 19.0 to 21.2 °C and 42.3 to 65.5% relative humidity. A photoperiod of 12 hours light from approximately 6 a.m. to 6 p.m. was maintained.

Acclimation Period

The animals were isolated upon arrival and allowed to acclimate for a period of 5 days. Animals were judged to be healthy prior to testing.

Feed

Certified High Fiber Rabbit Diet (PMI #5325) was available *ad libitum*. Feed containers were cleaned weekly and refilled at least once a week. No known contaminants which would interfere with the outcome of this study were present in the feed. Analyses of feed are maintained on file within the testing laboratory.

Husbandry, continued

Water

Water was available *ad libitum* through an automatic watering system. The source of the water was the local public water system. There have been no contaminants identified in previous water analyses that would be expected to interfere with the conduct of the study. Semiannual analyses of water are maintained on file within the testing laboratory.

Identification

Upon arrival, all rabbits were identified by uniquely-numbered ear tags. Cage cards contained the study-specific animal number and the ear tag number.

Experimental Design

Test Procedures

This study was conducted according to the Organisation for Economic Cooperation and Development (OECD) Guidelines for Testing of Chemicals: Guideline 404, Acute Dermal Irritation/Corrosion; and European Economic Community (EEC): Annex V., Test B.4, Acute Toxicity (Skin Irritation).

Identification Numbers of Animals Used

Animal numbers 439, 440, and 441 were used in this study.

Preparation of Test Substance

The test substance, a liquid, was administered as received.

Test Substance Exposure

The hair was removed from an area of the dorsal skin with an electric clipper. A single dose of 0.5 milliliter of the test substance was applied topically to each animal using a fiber pad. An occlusive wrap was used to hold the pad with the test substance in place for a period of four hours. At the end of the exposure period, the application site was rinsed with running water.

Vehicle

No vehicle was used.

Experimental Design, continued

Control Substance

No control substance was used. Adjacent areas of untreated skin of each animal served as control sites for the test areas.

Clinical Observations

The site of application was examined at 1, 24, 48, 72 hours and 7 days after removal of the occlusive patch. Observations included estimation of erythema, edema, necrosis, eschar formation, scarring, erosion, and staining caused by the test substance as well as general systemic effects.

Grading the Irritant Response

The most severely affected area within the sites of application of the test substance were examined and grades of dermal reactions recorded for each animal at all observation periods. Skin reactions were graded and scored as described in Table 1.

TABLE 1

Grading Of Skin Reaction[1]

Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation	4
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1.0 mm)	3
Severe edema (raised more than 1.0 mm and extending beyond area of exposure)	4

[1] Graded as described in OECD Guideline 404 (Annex V., Test B.4) (Grading of Skin Reaction)

Grading Other Clinical Observations

Other serious skin lesions, signs of abnormality, or toxic effects were graded and scored as described in Table 2.

Experimental Design, continued

Grading Other Clinical Observations, continued

TABLE 2

Grading Of Other Clinical Observations

Degree of Severity	
Very Slight	1
Slight	2
Moderate	3
Severe	4

Body Weights

Body weights were measured on the day of initiation of the study.

Necropsy

No necropsies were conducted at the conclusion of the 72-hour observation period.

Data Storage

The final report, data sheets, all nonperishable raw data, and an aliquot of the test substance have been stored in the testing facility archive managed under GLP-mandated conditions.

Protocol and Standard Operating Procedure Deviations

The were no SOP or protocol deviations during the study.

RESULTS

Observations for Skin Irritation/Corrosion

The application site of each animal was examined for signs of irritation at 1, 24, 48, 72 hours and 7 days after termination of exposure to the test substance. Observations for irritation (erythema, edema) are listed in Table 3.

TABLE 3

Observations For Skin Irritation

ANIMAL NUMBER	ERYTHEMA, EDEMA[1]				
	1 HOUR	24 HOURS	48 HOURS	72 HOURS	7 DAYS
439	3,0	3,1	4[2],1	4[2],1	0,0[3]
440	1,0	0,0	0,0	0,0	0,0
441	1,0	1,0	0,0	0,0	0,0

[1] Graded as described in OECD Guideline 404 (Annex V., Test B.4) (Grading of Skin Reaction)

[2] Erythema graded as "4" due to presence of slight eschar formation.

[3] A scar was present at the application site

Description of Serious Lesions and Irritation Other Than Erythema and Edema

Other dermal responses were limited to Rabbit 439. These included an area of necrosis (~2 cm^2) noted at the 1- and 24-hour examinations and erythema (grade 2) at the margins of the eschar formation at the 48- and 72-hour examinations.

Animal Welfare

After the observation of necrosis for Rabbit 439, benzocaine cream (20% by volume) was applied topically to the application site once on the day of dosing and twice on the day following test substance administration.

Toxic Effects

No toxic effects were noted during the study.

Body Weights

At initiation of the study, Rabbit Numbers 439, 440, and 441 weighed 2221, 2352, and 2448 grams, respectively.

DISCUSSION

In the dermal irritation study, signs of irritation for two of the three rabbits were limited to erythema (grade 1) at the 1-hour examination or the 1-hour and 24-hour examinations. For the remaining rabbit, erythema (grade 3) and necrosis were observed at the application site one hour after termination of exposure. At the 24-hour examination, erythema (grade 3), edema (grade 1), and necrosis were noted for this rabbit. For the 48- and 72-hour examinations, edema (grade 1) persisted while eschar formation (erythema -grade 4) was noted over the previous area of necrosis. Erythema (grade 2) was present at the margins of the eschar. On Day 7 of the study, only a scar was seen at the application site and the study was terminated.

CONCLUSION

Based on the irritant response observed, the test substance is considered to be corrosive to the skin and labeled as "causes burns" as defined in the 18th Adaptation of the EC Classification, Packaging, and Labelling of Dangerous Substances Directive.

REFERENCES

National Research Council (1996). *Guide for the Care and Use of Laboratory Animals.* National Academy Press. Washington, D.C.